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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,228	04/12/2001	Elaine L. Jacobson	NIAD-214.1 US	3352

24972 7590 05/07/2003

FULBRIGHT & JAWORSKI, LLP  
666 FIFTH AVE  
NEW YORK, NY 10103-3198

EXAMINER
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HUI, SAN MING R

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 05/07/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action**

Application No.

09/834,228

Applicant(s)

JACOBSON ET AL.

Examiner

San-ming Hui

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 April 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
  - (b) ☐ they raise the issue of new matter (see Note below);
  - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
  - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See attachment.

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attachment.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

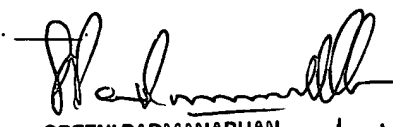
Claim(s) allowed: None.

Claim(s) objected to: None.

Claim(s) rejected: 30-37.

Claim(s) withdrawn from consideration: None.

8. ☐ The proposed drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s).
10. ☐ Other: \_\_\_\_\_

  
SREENI PADMANABHAN  
PRIMARY EXAMINER

5/2/03

**ADVISORY ACTION**

Continuation of 2):

The proposed amendments filed April 7, 2003 will not be entered as it will raised new issues and consideration for the Office. The proposed amendments filed April 7, 2003 will obviate the rejections under 35 USC 102(b) set forth in the previous office action. However, for the claims 31-33, the limitations were not addressed in the rejections under 35 USC 103 set forth in the previous office action mailed November 20, 2002. Because of this reason, the proposed amendments will necessitate a further consideration and a change of ground of rejection under 35 USC 103.

Continuation of 5):

Applicant's rebuttal arguments filed April 7, 2003 averring that the unexpected duration of octyl ester have been considered, but are not found persuasive. As discussed in the previous office action, the partition coefficient of octyl ester is higher than that of hexyl ester (due to the longer carbon chain length), and therefore the duration, which the residing time in the body would be expected to be longer, because of the hydrophobicity of the compound.

Applicant's further arguments filed April 7, 2003 averring longer the carbon chain length, lesser the vasodilating efficacy of the compound would be. Examiner notes that the residing time of a drug sometimes may not be equivalent to its efficacy. Please note that between the time that a drug is administered and the time it reaches to the site of activity, it must diffuse through a variety of biological membranes. The major criterion in

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evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil/water partition coefficient (See Remington Pharmaceutical Sciences, a well-known pharmaceutical handbook, that one of ordinary skill in the art is charged to have possession, page 1680, col. 1). The balance between the activity and the partition coefficient always exist (See Remington, page 1680, Fig. 91-5). There is an optimum partition coefficient for a drug at which it most effectively permeates membranes and shows greatest activity. If the partition coefficients of the compounds are less than the optimum value, it will result in decrease in lipid solubility and the drug will remain localized in the first aqueous phase it contacts. If the partition coefficients of the compounds are larger than the optimum value, it will result in increase lipid solubility but it will not be able to partition out of the lipid membrane once it gets in, and/or it reaches the maximum solubility in the lipid portion of the membrane. Therefore, one of ordinary skill in the art would expect that when the carbon chain length is getting longer, the vasodilating effect diminished, as Applicant's demonstrated in the response filed April 7, 2003.

Since the proposed amendments will not be entered, the rejections set forth in the previous office action mailed November 20, 2002 remain.

No unanswered rebuttal arguments are seen to be present.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui  
April 24, 2003